PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 95.83339/04	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2005/000616	International filing date *(day/month/year)* 18.02.2005	Priority date *(day/month/year)* 20.02.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K51/12		
Applicant ALGETA AS		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.03.2006	12.06.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 *epo nl* Fax: +31 70 340 - 3016	Authorized officer González Ramon, N. Telephone No. +31 70 340-3466

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000616

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-24	as originally filed
Claims, Numbers	
23-29	as originally filed
1-22	as amended (together with any statement) under Art. 19 PCT
Drawings, Sheets	
1/1	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 23-29
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 7-9,13-16
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-24 in part

because:

☒ the said international application, or the said claims Nos. 18-22 in relation to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 1-24 in part

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,3, 6-9, 12, 15, 17, 19, 20, 22
	No:	Claims	1, 4, 5, 10, 11, 13, 14, 16, 18, 21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	18-22 see separate sheet

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I
Basis of the report

The present report has been established as if some of the amendments had not been made since it has been considered they extend beyond the content of the international application as filed (Rule 70.2 © PCT).

The amendments concerned are the following: The subject matter of present claims 7-9, 13-16.

Present claim 7 reading: "with hydroxyapatite particulates **not containing magnetic iron**".

Present claim 13 reading: "hydroxyapatite **not containing magnetic iron**"

Said wording is not to be found in the originally filed documents contrary to Art. 19(2) PCT.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 18-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT:

Present claims 1-22 relate to compounds defined by reference to vague characteristics or properties, namely: "cation that is bivalent or trivalent" (claim 3); "polyethyleneketones", "glass-ceramics", "epoxy" (claim 6); "an alpha emitting radionuclide" (claim 17). In fact, the claims contain so many options, variables and possible permutations that a lack of clarity within the meaning of Article 6 PCT arises.

The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Support is only to be found in the present application for those parts relating to the compounds effectively disclosed in the examples and those specifically mentioned by chemical name in claims 1, 3, 7, 9, 13.

Moreover claim 17 encompass a genus of compounds defined only by their function: "in vivo generator for an alpha emitting radionuclide" (claim 17) wherein the relationship between the structural features of the members of the genus and said function have not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Therefore, claims 1-22 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

No opinion will be formulated in respect of subject-matter which is not covered by the

search report (Rule 66.1(e) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 18-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The following documents (D) are referred to in this communication:

D1 : WO 01/28587 A (FERX INCORPORATED; RUDGE, SCOTT, RAYMOND; KURTZ, TERRI, LYNN; TAPOLSKY) 26 April 2001 (2001-04-26)
D2 : VERGOTE I. ET AL: GYNECOLOGIC ONCOLOGY, vol. 47, 1992, pages 366-372, XP008057114
D3 : UNNI P. R. ET AL: NUCLEAR MEDICINE AND BIOLOGY, vol. 29, 2002, pages 199-209, XP004334818

Novelty (Art 33 (2) PCT)

The subject-matter of claims 1, 4, 5, 10, 11, 13, 14, 16, 18, 21 is not new in the sense of Article 33(2) PCT. The reasons therefore are the following:

D1 discloses magnetic targeted carrier composed of iron and synthetic ceramic material (hydroxyapatite) for the targeted delivery of radioisotopes including 212Bi, 213Bi, 223Ra. Mean particle sizes are 0.1- 10.0 micrometer (see page 7, lines 10-15; page 17, lines 1-5; claims 1, 5, 7).
Consequently the subject matter of claims 1,4, 5, 10, 11, 13, 14, 16, 18, 21 is not new over D1.

Inventive step (Art 33(3) PCT)

Should the applicant overcome the above raised objections, an inventive step has to be demonstrated for the subject matter of present claims 1-22 (Art 33(3) PCT).

According to the description (page 2, lines 8-10, 25-35), the problem underlying the present invention is the side effects of high energy alpha emitters radiation together with the leakage of free radionuclide and the difficulty to prepare alpha emitter containing preparations.

As solution to this problem a composition comprising hydroxyapatite incorporating an alpha emitting radionuclide or an vivo generator for an alpha emitting radionuclide is proposed.

Document D2, which can be considered the closest prior art for the assessment of inventive step of the present application, already addresses the problem of side effects of high energy alpha emitters radiation, the leakage of free radionuclide and the difficulty to prepare alpha emitter containing preparations with the use of the a-emitter 211At bound on microspheres and its use for intracavitary radiotherapy (see abstract, page 371, col. 1). Furthermore the therapeutic efficacy of the alpha-emitter 211At bound on microspheres is compared with 90Y and 32P colloids in a murine intraperitoneal tumor model and found of improved efficacy (see discussion)

The difference between D2 and the subject matter of present claims is the particular use of hydroxyapatite as the alternative particulate substance forming part of the composition. Hydroxyapatite as such is not explicitly disclosed in D2.

D3 discloses the preparation and bioevaluation of 166Ho labelled hydroxyapatite (HA) particles for radiosynovectomy (see abstract, discussion).

Consequently the use of hydroxyapatite as a suitable material for preparing radiolabeled particles for radiosynovectomy is rendered obvious to the skilled person in view of D3.

Moreover obvious chemistry reaction modifications in order to achieve an optimisation of

the preparation of the particles adapted to the particular case of alpha emitting radioisotope is routine practice and common knowledge for the skilled person in the art (i.e from referenced documents on present description page 2, lines 10-15) and therefore cannot either serve as conferring an inventive step to the subject matter of the present application.

Furthermore, the attention of the applicant is also drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step.
When the inventive step is solely based on the achievement of a technical effect, such as the rapid onset together with a sustained activity in vivo, substantially all embodiments should exhibit this effect.

However, it is evident that the number of compounds comprising groups encompassed under "cation that is bivalent or trivalent" (claim 3); "polyethyleneketones", "glass-ceramics", "epoxy" (claim 6); "an alpha emitting radionuclide" (claim 17); "in vivo generator for an alpha emitting radionuclide" (claim 17) is such that it is unlikely that all of them posses the effect claimed.

Therefore, as part of the subject matter of claims 1-22 does not exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step.

Consequently an inventive step for the subject matter of claims 1-22 cannot be acknowledged.